# METHOD AND APPARATUS FOR ANTENATAL RISK ASSESSMENT FOR CHROMOSOMAL ABNORMALITIES FACTORING IN MATERNAL AGE INFLUENCE

This is a continuation of application Ser. No. 08/275,180, filed Jul. 14, 1994 and now abandoned, which is hereby incorporated by reference.

## FIELD OF THE INVENTION

This invention relates to a method for antenatal screening for chromosomal abnormalities and to an apparatus for performing the method. In particular, it relates to a method and apparatus for antenatal screening for Down Syndrome.

## BACKGROUND OF THE INVENTION

The risk of Down Syndrome and some other chromosomal abnormalities in an unborn child is known to increase with the age of the mother and it is this knowledge which forms the basis for selection of pregnant women for further investigation. Further investigation for instance in the case of Down Syndrome involves sampling of the amniotic fluid by amniocentesis, a procedure which itself carries a risk for the mother, induction of a miscarriage being a recognized hazard of this procedure.

Maternal serum and other markers for Down Syndrome are widely used for antenatal screening for this chromosomal abnormality, the most common of these markers being alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG)—either the intact molecule thereof or its beta subunit—and unconjugated estriol (UE). Disclosures relating to the use of these markers in antenatal screening for Down Syndrome include U.S. Pat. No. 4,874,693, WO 89/00696 and WO 90/08325.

Maternal serum screening is based on selecting a subgroup of women who are at the greatest risk of giving birth to a child with an abnormality, in whom the risks of an invasive diagnostic procedure are considered to be outweighed by the risk of the abnormality. The risk is calculated by multiplying the age related risk by the likelihood ratio. The likelihood ratio is calculated from the relative frequencies of the multivariate Gaussian distribution functions of marker analytes in affected and unaffected pregnancies, corresponding to the value of the individual serum marker concentrations.

Since the concentrations of the various analytes vary with gestational age, the analyte concentrations must be normalized. This is performed by dividing the concentration of the analyte by the median concentration expected for that particular gestational age in women with unaffected pregnancies. This is termed the multiple of the median (MoM).

The use of two or more markers together in antenatal screening can be advantageous. For example the markers AFP, hCG and UE can be used together. The combination of marker analytes gives significantly more information than is given by any single marker alone, or by the group of markers when used sequentially. The use of likelihood ratios derived from a multivariate combination is an efficient means of deriving information relating to a woman's risk of carrying an affected child.

Hitherto it has generally been assumed that information relating to a woman's risk of carrying an unaffected child which is derived from markers such as AFP, hCG and UE is independent of maternal age. We believe that this assumption is correct with AFP and hCG and in many other instances. However in some instances, and particularly with UE, the assumption is not correct and the information relating to risk is influenced by maternal age. Therefore when using markers such as UE, allowance should be made for maternal age when processing any information which is obtained.



## SUMMARY OF THE INVENTION

According to the present invention we provide a method for antenatal screening for one or more predetermined chromosomal abnormalities comprising:

measuring one or more barkers, precursors or metabolites of the markers in a body fluid sample of a pregnant patient,

comparing the measured level of the one or more markers, precursors or metabolites of the markers and the gestational age of the fetus of the patient to reference values of the one or more markers, precursors or metabolites of the markers at various gestational ages, whereby allowance in the comparing is made for the maternal age of the patient,

the reference values being obtained from (a) pregnant women carrying fetuses having the one or more predetermined abnormalities, and from (b) pregnant women carrying normal fetuses, and

the comparison being indicative of the risk of the patient carrying a fetus with the one or more predetermined chromosomal abnormalities.

This invention also provides an apparatus comprising:

means adapted for receiving measurements of one or more markers or precursors or metabolites of the markers useful for antenatal screening for one or more chromosomal abnormalities in a body fluid sample of a pregnant patient, and

computer means for comparing the measurements to sets of reference data obtained from (a) pregnant women carrying fetuses having the one or more predetermined chromosomal abnormalities, and from (b) pregnant women carrying normal fetuses, the computer means also adjusting the level of the markers or precursors or metabolites of the markers for the maternal age of the patient.

The present invention provides a more accurate risk assessment of antenatal screening results because the maternal age of the patient is considered in evaluating the results from various common screening markers, and especially the results from UE determinations.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram of frequency against AFP MoM (log scale);

FIG. **2** is a diagram of frequency against hCG MoM (log scale);

FIG. **3** is a diagram of frequency against UE MoM (log scale);

FIG. **4** is a plot of UE MoM (log scale) against maternal age at date of delivery for data from Trials A in Example 1;

FIG. **5** is a plot of AFP MoM (log scale) against maternal age at date of delivery for data from Trials A in Example 1;

FIG. **6** is a plot of hCG MoM (log scale) against maternal age at date of delivery for data from Trials A in Example 1;

FIG. **7** is a plot of UE MoM (log scale) against maternal age at date of delivery for data from Trials B in Example 1;

FIG. **8** is a plot of AFP MoM (log scale) against maternal age at date of delivery for data from Trials B in Example 1;